American Journal of Medical Genetics 68:12–17 (1997)

Bronchopulmonary-Foregut Malformations: A Continuum of Paracrine Hamartomas?

Boris G. Kousseff,* Enid Gilbert-Barness, and Diane Debich-Spicer
Division of Medical Genetics and Department of Pathology, University of South Florida, Tampa, Florida

The bronchopulmonary-foregut malformations (BPFM) are usually sporadic, solitary cystic hamartomas involving conducting airways, arteries, venous drainage, and lung parenchyma. Transitional, compound hamartomas exist, and only their morphology is well-known. Between 1984–1994 we encountered and studied 10 unrelated patients and a stillborn infant with BPFM (out of 24,000 families). Ten were diagnosed in utero and one at birth as having congenital cystic adenomatoid malformation of the lung (CCAML). Postnatally, two diagnoses (20%) were corrected to bronchogenic cyst (BC) and diaphragmatic hernia, respectively. Bilateral lung involvement was present in 1 patient, and in 2 there was a considerable macroscopic regression of the hamartoma. Histologic studies of the six resected CCAML confirmed the diagnosis and implied dysregulated paracrine growth with its cellular and extracellular growth factors, protooncogenes, oncogenes, cytokines, cell-adhesive molecules, and receptors of these regulatory peptides, and their complex interactions as developmental morphogens in time and space. Am. J. Med. Genet 68:12–17, 1997

KEY WORDS: bronchopulmonary-foregut malformations; paracrinopathies; paracrine growth factors; regulatory peptides; prenatal diagnosis of BPFM; congenital cystic adenomatoid malformation of the lung

INTRODUCTION

The congenital bronchopulmonary-foregut malformations (BPFM) [Gerle et al., 1968; Heithoff et al., 1976] are predominantly cystic hamartomas [Van Dijk and Wagenvoort, 1973; Graham et al., 1987], i.e., developmental tumor-like malformations involving all four components of the bronchial tree: conducting airways, arteries, venous drainage, and lung parenchyma [Clements and Warner, 1987; Luck et al., 1986; O'Rahilly and Muller, 1984]. Their name refers to their endoderm-mesenchyme derivation and their frequent association with anomalies of the gastrointestinal tract, diaphragm, and pulmonary and systemic arterial/venous systems [Leithiser et al., 1986; Gerle et al., 1968]. As determined by their chronogenetics, i.e., the developmental timetable of the components of the bronchial tree [Luck, et al., 1986; Reid, 1984], they occur during blastogenesis with continuing changes beyond week 16 of fetal development [Stovin, 1985; Luck et al., 1986; O'Rahilly and Muller, 1984]. They appear to be a continuum [Blesovsky, 1967; Demos and Teresi, 1975; Sade et al., 1974; Gerle et al, 1968], although in reports four fairly distinct types, congenital cystic adenomatoid malformation of the lung (CCAML), extra- and intralobar pulmonary sequestration (PS), congenital lobar overinflation (CLO) [Coran and Drongowski, 1994], synonymous with congenital pulmonary lobar emphysema, and bronchogenic cyst (BC), are discussed.

In addition, there are numerous reports of transitional and compound hamartomas with histologic findings of at least two of the four types [Aulicino et al., 1994; Coran and Drongowski, 1994; Demos and Teresi, 1975; Ng et al., 1994; Sakala et al., 1994; Zangwill and Stocker, 1993]. The compound lesions show overlapping clinical manifestations, despite morphologic distinctiveness of the participating hamartomas [Budorick et al., 1992; Demos and Teresi, 1975; Moerman et al., 1992; Zangwill and Stocker, 1993; Dolkart et al., 1992], while the four types have clinical and radiological/sonographic signs and symptoms that allow diagnostic differentiation without histologic studies. Most of these malformations are solitary, nonhereditary, and with normal chromosomes; yet they have been reported with trisomies 18 and 21 [Moerman et al., 1992; Levkoff et al., 1964; Bromley et al., 1995] and with 47,XXY [Revillon et al., 1993], in monochorionic diamnionic twins [Moerman et al., 1992; Rebarber and Mohan, 1992; Harper, 1992; Sandoz, 1907; Bromley et al., 1995], with monogenic traits such as urogenital adysplasia [Moerman et al., 1992] and brachymorphism-onychodysplasia-dysphalangism syndrome [Verloes

*Correspondence to: Boris G. Kousseff, M.D., Division of Medical Genetics, University of South Florida, 10770 North 46th Street, Suite C-900, Tampa, FL 33617-3451.

Received 6 July 1995; Accepted 26 April 1996.

et al., 1993], and with other hamartomas, Jadassohn sebaceous nevus [Sweeney et al., 1994], nephromegaly [Graham et al., 1987; Scully et al., 1985; Weinberg and Zumwalt, 1977], and renal cysts [Graham et al., 1987; Conway, 1951; Roloff et al., 1971]. In Proteus and basal-cell nevus syndromes there have also been pulmonary hamartomas resembling BPFM [Cohen, 1993; Totten, 1980]. Similar hamartomas have been reported with the oculoauriculovertebral spectrum [Bowen and Parry, 1980], with congenital heart defects [Lacina et al., 1981; Nishibayashi et al., 1981; Sakala et al., 1994], with diaphragmatic hernia [Miller et al., 1980; Luet'ic et al., 1995; Ryan et al., 1995], and with esophageal and jejunal atresias [German et al., 1976; Birdsell et al., 1966]. An assortment of major anomalies including facial clefts, hydrocephaly, and neural tube defects was found in several of 132 patients with BPFM [Thorpe-Beeston and Nicolaides, 1994].

There are several reports of familial BPFM [MacRae, 1947; Sandoz, 1907; Krous and Sexauer, 1981]. CCAML is the most frequently diagnosed pulmonary hamartoma in utero [Heydanus et al., 1993; Petit et al., 1987; Boulot et al., 1991; Rebarber and Mohan, 1992; Revillon et al., 1993; Sakala et al., 1994; Kuller et al., 1992], and may be the most common postnatal lesion [Coran and Drongowski, 1994; Bailey et al., 1990; Cloutier et al., 1993; Richards et al., 1992; Revillon et al., 1993]. On histologic examination, three types of CCAML have been delineated [Stocker et al., 1977], and recently, based on the site of the defect in the tracheobronchial tree, Stocker [1994] expanded his classification to five types, with types 0 and 4 being exceedingly rare. Traditionally, Roman numerals are used to designate the types, though Arabic numerals are also used. Renal agenesis/dysplasia is the most commonly associated anomaly with CCAML type 2 [Petit et al., 1987; Zangwill and Stocker, 1993; Neilson et al., 1991; Krous et al., 1980], and CCAML has been reported with prune-belly syndrome [Kuruvilla et al., 1987; Weber et al., 1978; Sakala et al., 1994; Wilson et al., 1978]. Currently, the aforementioned statements are universally accepted, yet it took over a century from the initial reports of the hamartomas [Bartholinus, 1687; Rokitansky, 1861; Rektorzik, 1861; Stoerk, 1897], and as many as 40 hypotheses for their origin and pathogenesis [Savic et al., 1979; Gerle et al., 1968; Biancalana, 1963], along with the use of numerous synonyms [Clements and Warner, 1987; Carter, 1969], for conceptual agreements to be reached. However, several aspects, particularly in regard to cause and pathogenesis, still require better understanding. Also, a forgotten issue, i.e., possible malignant degeneration of these hamartomas [Sheffield et al., 1987; Korol, 1953; McKusick and Fisher, 1958; Stephanopoulos and Catsaras, 1963; Krous and Sexauer, 1981; Weinberg et al., 1980; Benjamin and Cahill, 1991; Ribet et al., 1995], should remain in focus as relevant to the pathogenesis and comparable degeneration of hamartomas in other conditions/phakomatoses [Kousseff, 1992, 1995]. A review of the pathology of these malformations, with emphasis on pathogenesis in conjunction with analysis of 10 unreported patients and a stillborn infant with CCAML, should contribute further knowledge about the pulmonary hamartomatous malformations and hamartomas in general [Kousseff, 1990, 1992].

MATERIALS, METHODS, AND RESULTS

Between January 2, 1984–October 31, 1994, through the University of South Florida Regional Genetics Program, 10 unrelated patients and a stillborn infant with BPFM were encountered and studied (Table I). They were among the 24,000 families evaluated during this period through the clinical and prenatal sections of the program. Seven were males and 4 females, and 4 of them (3 males and 1 female) had trypsin Giemsa-banded karyotypes; all were normal. Nine patients were of adequate size for gestational age, with 2 born prematurely, and 2 were large for term-gestation. The ethnic distribution of the patients was 8 Caucasians, 2 African-Americans, and 1 Hispanic. Ten of 11 were diagnosed prenatally during the second or third trimester by level II fetal sonography as CCAML, at a mean of 20.5 weeks of gestation (range, 17–26 weeks). Two of 10 (20%) were misdiagnosed, patient 9 had a BC at birth, and patient 10 had a left diaphragmatic hernia instead of CCAML. In patients 2 (Fig. 1) and 3 there was macroscopic regression of the CCAML (20%), and at birth both patients were asymptomatic with unremarkable chest radiograms. In 7 patients the hamartomas were on the left, in 2 they were on the right, and in patient 5, a stillborn, fetal sonograms showed left upper and lower lobes CCAML type 1; at autopsy an additional small CCAML type 1 was found in the right middle lobe. More than one ipsilateral lobe was involved in 3 patients. Patient 9 with BC had two needle-cyst aspirations in utero, and amniography in this patient did not show a communication with the gastrointestinal tract. Abruptio placentae and placenta praevia were each encountered once (patients 6 and 7). In two pregnancies there was gestational class A_1 diabetes mellitus, and one of these infants, patient 11, was large for gestational age without anomalies other than CCAML. Patient 7 was diagnosed at birth.

There was a mediastinal shift in 9/11 patients, and at birth 6/10 had tachypnea and dyspnea. In 2/6, extracorporal membrane oxygenation (ECMO) was utilized. Patient 10, with diaphragmatic hernia, benefited from it, while patient 6 developed massive bilateral intraventricular hemorrhage with subsequent hydrocephaly, ventriculoperitoneal shunt, and considerable developmental delay. Other pulmonary/thoracic anomalies included lung hypoplasia and pneumothorax in 2/11 each, and pulmonary hypertension, thoracic asymmetry, and pectus excavatum in one each. Hydrops with polyhydramnios was present in 2/11: one (patient 5) was stillborn, and the other (patient 11) did well after lobectomies. Five of the 10 liveborn patients needed lobectomy, and one (patient 10) had his left diaphragmatic hernia repaired. The long-term results of the surgeries were excellent. Histologic studies of the five excised CCAML and the autopsy of the stillborn confirmed the preoperative diagnoses; 2 showed CCAML type 1, and 4 showed CCAML type 2. As expected, type 1 showed multiple large cysts communicating with the

TABLE I. Summary of Sonographic and Clinical Manifestations*

Patient no.	Type of hamartoma	Age at diagnosis	Presentation	Outcome
1.	CCAML 2, left UL, LL	17 wk, US	MS, RD	Well after lobectomy
2.	CCAML 1, right UL, LL	20 wk, US	Asymptomatic	CCAML regression
3.	CCAML 1, left LL	18 wk, US	Asymptomatic	CCAML regression
4.	CCAML 2, left LL	19 wk, US	MS, asymptomatic	Well after lobectomy
5.	CCAML 1, left UL, LL, right ML	25 wk, US	MS, polyhydramnios, anasarca	Stillborn
6.	CCAML 2, left LL	19 wk, US	MS, RD	ECMO, IVH, hydrocephaly, RD
7.	CCAML 1, left UL	Birth	MS, RD	Well after lobectomy
8.	CCAML 2, right LL	18 wk, US	MS, RD	Well after lobectomy
9.	CCAML 2, left LL postnatally BC	20 wk, US	MS, asymptomatic	Well
10.	CCAML 2, left LL postnatally diaphragmatic hernia	26 wk, US	MS, RD	ECMO, well after hernia repair
11.	CCAML 2, right UL, ML, LL	22 wk, US	MS, polyhydramnios, RD, hydrops	Well after lobectomy

*UL, upper lobe; LL, lower lobe; ML, middle lobe; wk, weeks; US, ultrasound; MS, mediastinal shift; RD, respiratory distress; IVH, intraventricular hemorrhage; ECMO, extracorporal membrane oxygenation.

bronchial tree of the affected lobe(s). A smooth or wrinkled glistening membrane lined the cysts. Microscopically, the membrane showed ciliated columnar-to-pseudostratified tall columnar epithelium overlying a thin-to-moderately-thick fibromuscular layer. The amount of elastic tissue was increased. Occasional clusters of mucogenic cells were present along the walls of the cysts or in the alveoli of the adjacent parenchyma. In type 2 there were multiple, evenly-spaced cysts that rarely exceeded 1.2 cm in diameter. The cysts communicated with the bronchial tree and contained air in the liveborn children. Smooth or wrinkled glistening membranes lined the cysts. Microscopically, the cysts bore close resemblance to dilated terminal bronchials. They were lined with ciliated cuboidal-to-columnar epithelium overlying a fibromuscular layer. Elastic tissue was present. Mucus-secreting cells were not found. Occasional striated muscle fibers were encountered. None of the hamartomas showed malignant degeneration.

DISCUSSION

As is almost always the case, large series of new patients with rare anomalies/disorders lead to critical review of current knowledge about the anomalies, and

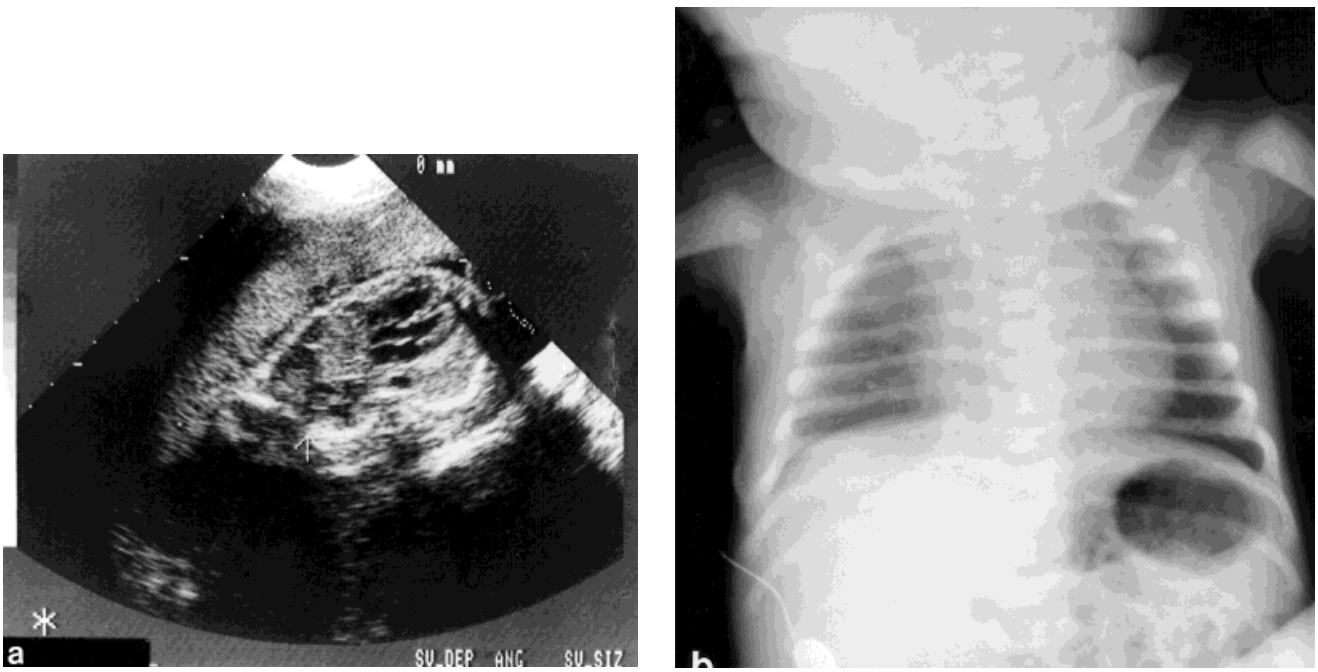

Fig. 1. Patient 2. **a**: Level II fetal sonogram at 28 weeks of gestation, showing right multicystic CCAML (arrow), measuring 2.8 × 2.3 cm; at 33 and 36 weeks the CCAML showed a regression in size, to 2.6 × 2 × 2 cm and 1.4 × 0.8 × 0.5 cm, respectively. **b**: Chest radiogram at birth. No evidence of CCAML.

an update with expansion of knowledge in order to better understand the pathogenesis. Indeed, the reported 10 patients and the stillborn with CCAML have allowed us to address unresolved issues such as spontaneous regression of CCAML/BPFM, unilateral vs. bilateral lung involvement, accuracy of prenatal and postnatal diagnosis, association with other anomalies/conditions, relevant clinical manifestations to short- and long-term prognosis, applicability of therapeutic modalities, and pathogenesis.

In 1983, progress in BPFM prenatal diagnosis led to the first report of spontaneous regression of CCAML in utero [Glaves and Baker, 1983]. Similar reports followed [Revillon et al., 1993; Heydanus et al., 1993; Kuller et al., 1992; Hatjis and Wall, 1992; McCullagh et al., 1994; Budorick et al., 1992], and as indicated by this series as many as 20% of hamartomas may show macroscopic regression in utero.

Even in recent reports [Cloutier et al., 1993], bilateral BPFM are still considered exceedingly rare. This was not so in this series, with 1/11 having bilateral CCAML 1, or in the extensive literature review [Miller et al., 1980; Meagher et al., 1993; Haddon and Bowen, 1991; Revillon et al., 1993; Petit et al., 1987; Neilson et al., 1991; Heydanus et al., 1993; McKusick and Fisher, 1958; Chao and Monoson, 1990; Schenck, 1937; Levkoff et al., 1964; Willius, 1937; Numabe et al., 1994; Murray et al., 1994; Walker and Cudmore, 1990; Rempen et al., 1987]. In other words, bilateral lung involvement should be anticipated and looked for.

In this study, an error in the prenatal diagnosis of BPFM occurred twice (20%). In patient 9, a BC at birth was diagnosed prenatally as CCAML type 2. Since he did not require postnatal lobectomy, it was impossible to determine whether or not the two prenatal needle aspirations had anything to do with the change of sonographic, i.e., macroscopic appearance of the hamartoma. Also, we do not know yet if the lesion communicates with the tracheobronchial tree as CCAML does, in contradistinction to a BC that should not have such communication [Nishibayashi et al., 1981; Bailey et al., 1990]. Patient 10, with left diaphragmatic hernia, was misdiagnosed as having CCAML type 2 by a single sonogram through our institution, and the lack of reevaluation is probably the source of the diagnostic error. The erroneous diagnoses in 20% of the patients underlie the necessity for cautious interpretation of initial sonographic findings and the need for reevaluations whenever a diagnosis of BPFM is suspected. In regard to prognosis and genetic counseling, a cautious approach was best for patient 11 as well. At 23 weeks of gestation this patient had extensive ipsilateral involvement of the lung, polyhydramnios, hydrops, and mediastinal shift. The unfavorable prognostic impression was conveyed to the family. However, the fetus reached term and with postnatal lobectomies did very well. In other words, caution again was the better part of valor, although our study did not indicate a need to avoid a type-specific prenatal diagnosis of BPFM, as has been recommended [McCullagh et al., 1994].

Since none of the studied patients had nonpulmonary/nonthoracic-associated anomalies, issue to such anomalies could not be taken. In the literature on associated anomalies in BPFM there is a prevalence range from 12–26% [Thorpe-Beeston and Nicolaides, 1994; Stocker et al., 1977; Cloutier et al., 1993], and there was a considerable ascertainment/selection bias in determining this range. However, there is a consensus that within BPFM types, extralobar PS and CCAML type 2 more frequently have associated anomalies [Cloutier et al., 1993; Savic et al., 1979]. Additional studies are needed if an accurate prevalence figure is to be obtained.

While in this study none of the histologic specimens showed malignant changes, the issue of malignant degeneration within BPFM remains important. Current practice of early postnatal lobectomies for hamartomas most likely accounts for the few recent reports of malignancies within BPFM [Murphy et al., 1991; Sheffield et al., 1987]. On the other hand, previous reports have shown that such degeneration is a part of the phenotype [McKusick and Fisher, 1958; Stephanopolous and Catsaras, 1963; Krous and Sexauer, 1981; Weinberg et al., 1980; Ueda et al., 1977; Korol, 1953; Womack and Graham, 1941; Huntington et al., 1963; Benjamin and Cahill, 1991; Ribet et al., 1995]. Ever since Korol [1953] found bronchogenic carcinoma in 9% of adult autopsies with BPFM of a particular type, "congenital cystic emphysema" vs. 1.5% in autopsies without BPFM, predilection to malignancies is considered established. Based on that, early resection of the hamartomas is recommended [Hedlund et al., 1989; Coran and Drongowski, 1994; Sheffield et al., 1987]. On the other hand, the in utero regression of BPFM precluding the necessity of lobectomy poses a dilemma, i.e., whether or not presumed remaining pulmonary microscopic changes require long-term monitoring for malignant degeneration and even prophylactic lobectomy. While most of the malignancies have been bronchogenic carcinomas [Korol, 1953; Huntington et al., 1963; Womack and Graham, 1941; Stephanopolous and Catsaras, 1963; Sheffield et al., 1987; McKusick and Fisher, 1958], just as in other hamartomatous conditions/phakomatoses [Kousseff, 1992] a variety of unusual rare malignancies has been reported: myxosarcomas [Ueda et al., 1977; Stephanopolous and Catsaras, 1963], rhabdomyosarcomas [Krous and Sexauer, 1981; Weinberg et al., 1980; Murphy et al., 1991], reticulosarcoma [Ueda et al., 1977], hemangiopericytoma [Krous and Sexauer, 1981], and mesenchymal sarcoma [Hedlund et al., 1989]. From the reports it is not clear how a benign developmental tumor-like lesion most likely due to dysregulated paracrine growth of differentiated mature cells and extracellular matrix (ECM) [Kousseff, 1992, 1995] switches to the autocrine growth mechanism responsible for the malignant degeneration. On the other hand, both mechanisms intertwine and are based on cell-to-cell communications and interactions through the various growth factors/regulatory peptides, their receptors, and the ECM.

As to pathogenesis, the fact that BPFM are congenital, sporadic, phenotypically-overlapping hamartomas, encountered in a number of different conditions, some chromosomal or hereditary, indicates that regardless of cause(s), dysregulated cell/ECM growth during embryogenesis plays a major pathogenetic role. The over/undergrowth of the lesions appears to be through

the paracrine growth mechanism, engaging through cellular transformation the autocrine growth mechanism in case of malignant degeneration. In other words, at cellular and ECM levels the hamartomas imply dysregulated paracrine growth, i.e., dysregulated growth factors, protooncogenes, oncogenes, cytokines, cell-adhesive molecules, the receptors of these regulatory peptides, and their complex interactions as developmental morphogens in time and space. Epidermal and insulin-like growth factors known to play a major role in lung development may be particularly pertinent to the pathogenesis of BPFM. The latter appear to represent a continuum of paracrine anomalies and in the near future, through immunocytochemistry, determination of RNA concentrations, in situ hybridization studies, and Northern blotting, a confirmation of their pathogenesis is expected.

ACKNOWLEDGMENTS

We thank Ms. Hazel Burns for her excellent work on the manuscript.

REFERENCES

Aulicino MR, Reis ED, Dolgin SE, Unger, PD, Kumudini DS (1994): Intra-abdominal pulmonary sequestration exhibiting congenital cystic adenomatoid malformation. Arch Pathol Lab Med 118: 1034–1037.

Bailey PV, Tracy T, Connors RH, de Mello D, Lewis JE, Weber TR (1990): Congenital bronchopulmonary malformations. J Thorac Cardiovasc Surg 99:597–603.

Bartholinus T (1687): De Pulmonibus. In Malpighi M (ed): "Opera Omnia." London: R. Littlebury, pp 349–350.

Benjamin DR, Cahill JL (1991): Bronchioloalveolar carcinoma of the lung and congenital cystic adenomatoid malformation. Am J Clin Pathol 95:889–892.

Biancalana L (1963): Die Lungenzysten. Thoraxchirurgie 11:511–531.

Birdsell DC, Wentworth P, Reilly BJ, Donohue WL (1966): Congenital cystic adenomatoid malformation of the lung: A report of eight cases. Can J Surg 9:350–356.

Blesovsky A (1967): Pulmonary sequestration, a report of an unusual case and a review of the literature. Thorax 22:351–357.

Boulot P, Pages A, Deschamps F, Hedon B, Laffargue F, Viala JL (1991): Early prenatal diagnosis of congenital cystic adenomat oid malformation of the lung (Stocker's type I); a case report. Eur J Obstet Gynecol Reprod Biol 41:159–162.

Bowen AD, Parry WH (1980): Bronchopulmonary foregut malformation in the Goldenhar anomalad. AJR 134:186–188.

Bromley B, Parad R, Estroff JA, Benacerraf BR (1995): Fetal lung masses: Prenatal course and outcome. J Ultrasound Med 14: 927–936.

Budorick NE, Pretorius DH, Leopold GR, Stamm ER (1992): Spontaneous improvement of intrathoracic masses diagnosed *in utero.* J Ultrasound Med 11:653–662.

Carter R (1969): Pulmonary sequestration. Ann Thorac Surg 7:68–83.

Chao A, Monoson RF (1990): Neonatal death despite fetal therapy for cystic adenomatoid malformation: A case report. J Reprod Med 35:655–657.

Clements BS, Warner J (1987): Pulmonary sequestration and related congenital bronchopulmonary-vascular malformations: Nomenclature and classification based on anatomical and embryological considerations. Thorax 42:401–408.

Cloutier MM, Schaeffer DA, Hight D (1993): Congenital cystic adenomatoid malformation. Chest 103:761–764.

Cohen MM (1993): Proteus syndrome: Clinical evidence for somatic mosaicism and selective review. Am J Med Genet 47:645–652.

Conway DJ (1951): Origin of lung cysts in childhood. Arch Dis Child 26:504–529.

Coran AG, Drongowski R (1994): Congenital cystic disease of the tracheobronchial tree in infants and children. Arch Surg 129: 521–527.

Demos NJ, Teresi A (1975): Congenital lung malformations. A unified concept and a case report. J Thorac Cardiovasc Surg 70:260–264.

Dolkart LA, Reimers FT, Helmuth WV, Porte MA, Eisinger G (1992): Antenatal diagnosis of pulmonary sequestration: A review. Obstet Gynecol Surv 47:515–520.

Gerle RD, Jaretzki A III, Ashley CA, Berne AS (1968): Congenital bronchopulmonary-foregut malformation. N Engl J Med 278: 1413–1419.

German JC, Mahour GH, Woolley MM (1976): Esophageal atresia and associated anomalies. J Pediatr Surg 11:299–306.

Glaves J, Baker JL (1983): Spontaneous resolution of maternal hydramnios in congenital adenomatoid malformation of the lung. Antenatal ultrasound features. Br J Obstet Gynaecol 90:1065–1068.

Graham JM Jr, Boyle W, Troxell J, Cullity GJ, Sprague PL, Beckwith JB (1987): Cystic hamartomata of lung and kidney: A spectrum of developmental abnormalities. Am J Med Genet 27:45–59.

Haddon MJ, Bowen A (1991): Bronchopulmonary and neurenteric forms of foregut anomalies. Radiol Clin North Am 29:241–254.

Harper A (1992): Prenatal diagnosis of cystic adenomatoid malformation of the lung in a twin pregnancy. Ulster Med J 61:102–105.

Hatjis CG, Wall P (1992): Type II congenital cystic adenomatoid malformation of the lung with a mediastinal shift. J Reprod Med 37:753–756.

Hedlund GL, Bisset GS, Bove KE (1989): Malignant neoplasms arising in cystic hamartomas of the lung in childhood. Radiology 173:77–79.

Heithoff KB, Sane SM, Williams HJ, Jarvis CJ, Carter J, Kane P, Brennom W (1976): Bronchopulmonary foregut malformations: A unifying etiological concept. AJR 126:46–55.

Heydanus R, Stewart PA, Wladimiroff JW, Los FJ (1993): Prenatal diagnosis of congenital cystic adenomatoid lung malformation: A report of seven cases. Prenat Diagn 13:65–71.

Huntington HW, Poppe JK, Goodman MJ (1963): Carcinoma arising in a congenital cyst of the lung. Dis Chest 329–332.

Korol E (1953): The correlation of carcinoma and congenital cystic emphysema of the lungs. Dis Chest 23:403–411.

Kousseff BG (1990): The phakomatoses as paracrine growth disorders (paracrinopathies). Clin Genet 37:97–105.

Kousseff BG (1992): Hypothesis: Jadassohn nevus phakomatosis: A paracrinopathy with variable phenotype. Am J Med Genet 43: 651–661.

Kousseff BG (1995): Multiple endocrine neoplasia 2 (MEN 2)/MEN 2A (Sipple syndrome). Dermatol Clin 13:91–97.

Krous HF, Sexauer L (1981): Embryonal rhabdomyosarcoma arising within a congenital bronchogenic cyst in a child. J Pediatr Surg 16:506–508.

Krous HF, Harper PE, Perlman M (1980): Congenital cystic adenomatoid malformation in bilateral renal agenesis. Arch Pathol Lab Med 104:368–370.

Kuller JA, Yankowitz J, Goldberg JD, Harrison MR, Adzick NS, Filly RA, Callen PW, Golbus MS (1992): Outcome of antenatally diagnosed cystic adenomatoid malformations. Am J Obstet Gynecol 167:1038–1041.

Kuruvilla AC, Kesler KR, Williams JW, McGee MJ (1987): Congenital cystic adenomatoid malformation of the lung associated with prune belly syndrome. J Pediatr Surg 22:370–371.

Lacina S, Townley R, Radecki L, Stockinger F, Wyngaarden M (1981): Esophageal lung with cardiac abnormalities. Chest 79:468–470.

Leithiser RE Jr, Capitanio MA, Macpherson RI, Wood BP (1986): "Communicating" bronchopulmonary foregut malformations. AJR 146:227–231.

Levkoff AH, Mather GB, Eisenstein RP (1964): A case of trisomy 16–18. Am J Dis Child 107:300–303.

Luck SR, Reynolds M, Raffensperger JG (1986): Congenital bronchopulmonary malformations. Curr Probl Surg 23:245–314.

Luet'ic T, Crombleholme TM, Semple JP, D'Alton M (1995): Early prenatal diagnosis of bronchopulmonary sequestration with associated diaphragmatic hernia. J Ultrasound Med 14:533–535.

MacRae DF (1947): Congenital cystic disease of the lung. A familial incidence of four males in one family. Can Med Assoc J 57:545–550.

McCullagh M, MacConnachie I, Garvie D, Dykes E (1994): Accuracy of prenatal diagnosis of congenital cystic adenomatoid malformation. Arch Dis Child 71:111–113.

McKusick VA, Fisher AM (1958): Congenital cystic disease of the lung with progressive pulmonary fibrosis and carcinomatosis. Ann Intern Med 48:774–790.

Meagher SE, Fisk NM, Harvey JG, Watson GF, Boogert A (1993): Disappearing lung echogenicity in fetal bronchopulmonary malformations: A reassuring sign? Prenat Diagn 13:495–501.

Miller RK, Sieber WK, Yunis EJ (1980): Congenital adenomatoid malformation of the lung. A report of 17 cases and review of the literature. Pathol Annu 15:387–407.

Moerman P, Fryns JP, Vandenberghe K, Devliegers H, Lauweryns JM (1992): Pathogenesis of congenital cystic adenomatoid malformation of the lung. Histopathology 21:315–321.

Murphy JJ, Blair GK, Fraser GC, Ashmore PG, LeBlanc JG, Sett SS, Roger P, Magee JF, Taylor GP, Dimmik J (1991): Rhabdomyosarcoma arising within congenital pulmonary cyst: Report of three cases. J Pediatr Surg 27:1364–1367.

Murray ME, Given-Wilson RM, Christopher JA, Jeffrey IJM (1994): Bilateral communicating bronchopulmonary foregut malformations in an infant with multiple congenital anomalies. Pediatr Radiol 24:128–130.

Neilson IR, Russo P, Laberge JM, Filiatrault D, Nguyen LT, Collin PP, Guttman FM (1991): Congenital adenomatoid malformation of the lung: Current management and prognosis. J Pediatr Surg 26: 975–981.

Ng KJ, Hasan N, Gray ES, Jeffrey RR, Youngson GG (1994): Intralobar bronchopulmonary sequestration: Antenatal diagnosis. Thorax 49:379–380.

Nishibayashi SW, Andrassy RJ, Wooley MM (1981): Congenital cystic adenomatoid malformation: A 30-year experience. J Pediatr Surg 16:704–706.

Numabe H, Yamada N, Sasamoto M, Takei Y, Miyajima T, Hoshika A, Itoh H, Fujitoh J, Takada J, Nakajima A, Funayama H, Isaka K, Takayama M, Kudo M (1994): A case of nonimmune hydrops with bilateral type III congenital cystic adenomatoid malformation of the lung. Teratology 50:67 (abstract).

O'Rahilly R, Muller F (1984): Respiratory and alimentary relations in staged human embryos; new embryologic data and congenital anomalies. Ann Otol Rhinol Laryngol 93:421–429.

Petit P, Bossens M, Thomas D, Moerman P, Fryns JP, Van den Berghe H (1987): Type III congenital cystic adenomatoid malformation of the lung: Another cause of elevated alpha fetoprotein? Clin Genet 32:172–174.

Rebarber A, Mohan R (1992): Prenatal diagnosis of cystic adenomatoid malformation of one fetus in a twin pregnancy: An unusual presentation. J Ultrasound Med 11:305–308.

Reid L (1984): The lung: Its growth and remodeling in health and disease. Br J Dis Chest 78:113–134.

Rektorzik E (1861): Ueber accessorische Lungenlappen. Wochenbl Ges Aerzte (Wien) 17:4–6.

Rempen A, Feige A, Wünsch P (1987): Prenatal diagnosis of bilateral cystic adenomatoid malformation of the lung. J Clin Ultrasound 15:3–8.

Revillon DJ, Plattner V, Sonigo P, Dommergues M, Mandelbrot L, Dumez Y, Nihoul-Fékété (1993): Congenital cystic adenomatoid malformation of the lung: Prenatal management and prognosis. J Pediatr Surg 28:1009–1011.

Ribet ME, Copin M-C, Soots JG, Gosselin BH (1995): Bronchioloalveolar carcinoma and congenital cystic adenomatoid malformation. Ann Thorac Surg 60:1126–1128.

Richards DS, Langham MR, Dolson LH (1992): Antenatal presentation of a child with congenital lobar emphysema. J Ultrasound Med 11:165–168.

Rokitansky C (1861): Lehrbuch der pathologischen Anatomie. Wien W Braumuller 3:44–45.

Roloff DW, Baillie EE, Weaver DK (1971): Macrobullous medullary polycystic kidney and cystic lung disease—Report of a rare association in a child. Am J Dis Child 121:318–324.

Ryan CA, Finer NN, Etches PC, Tierney AJ, Peliowski A (1995): Congenital diaphragmatic hernia: Associated malformations—Cystic adenomatoid malformation, extralobular sequestration and laryngotracheoesophageal cleft: Two case reports. J Pediatr Surg 30:883–885.

Sade RM, Clouse M, Ellis FH Jr (1974): The spectrum of pulmonary sequestration. Ann Thorac Surg 18:644–658.

Sakala EP, Perrott WS, Grube GL (1994): Sonographic characteristics of antenatally diagnosed extralobar pulmonary sequestration and congenital cystic adenomatoid malformation. Obstet Gynecol Surv 49:647–654.

Sandoz E (1907): Ueber zwei Fälle von "Fötaler Bronchiektasie." Beitr Pathol Anat Allg Pathol 41:495–520.

Savic B, Birtel FJ, Tholen W, Funke HD, Knoche R (1979): Lung sequestration: Report of seven cases and review of 540 published cases. Thorax 34:96–101.

Schenck SG (1937): Diagnosis of congenital cystic disease of the lung. Arch Intern Med 60:1–21.

Scully RE, Mark EJ, McNeely BU (1985): Case records of the Massachusetts General Hospital: Weekly clinicopathologic exercises. N Engl J Med 313:374–382.

Sheffield EA, Addis BJ, Corrin B, McCabe MM (1987): Epithelial hyperplasia and malignant change in congenital lung cysts. J Clin Pathol 40:612–614.

Stephanopoulos C, Catsaras H (1963): Myxosarcoma complicating a cystic hamartoma of the lung. Thorax 18:144–145.

Stocker JT (1994): An expanded concept of cystic lung disease in children. Presented at the 16th Annual Aspen Conference on Pediatric Disease, Aspen, Colorado, August 1–5.

Stocker JT, Madewell JE, Drake RM (1977): Congenital cystic adenomatoid malformation of the lung: Classification and morphologic spectrum. Hum Pathol 8:155–171.

Stoerk O (1897): Ueber angeborene blasige Missbildung der Lunge. Wien Klin Wochenschr 10:25–31.

Stovin PGI (1985): Early lung development. Editorial. Thorax 40: 401–404.

Sweeney WJ, Kuller JA, Chescheir NC, Veness-Meehan K (1994): Prenatal ultrasound findings of linear nevus sebaceous and its association with cystic adenomatoid malformation of the lung. Obstet Gynecol 83:860–862.

Thorpe-Beeston JG, Nicolaides KH (1994): Cystic adenomatoid malformation of the lung: Prenatal diagnosis and outcome. Prenat Diagn 14:677–688.

Totten JR (1980): The multiple nevoid basal cell carcinoma syndrome: Report of its occurrence in four generations of a family. Cancer 46:1456–1462.

Ueda K, Gruppo R, Unger F, Martin L, Bove K (1977): Rhabdomyosarcoma of lung arising in congenital cystic adenomatoid malformation. Cancer 40:383–388.

Van Dijk C, Wagenvoort CA (1973): The various types of congenital adenomatoid malformation of the lung. J Pathol 110:131–134.

Verloes A, Bonneau D, Guidi O, Berthier M, Oriot D, Van Maldergem L, Koulischer L (1993): Brachymorphism-onychodysplasia-dysphalangism syndrome. J Med Genet 30:158–161.

Walker J, Cudmore RE (1990): Respiratory problems and cystic adenomatoid malformation of lung. Arch Dis Child 65:649–650.

Weber ML, Rivard G, Perreault G (1978): Prune belly syndrome associated with congenital cystic adenomatoid malformation of the lung. Am J Dis Child 132:316–317.

Weinberg AF, Zumwalt RE (1977): Bilateral nephromegaly and multiple pulmonary cysts. Am J Clin Pathol 67:284–288.

Weinberg AG, Currarino G, Moore GC, Votteler TP (1980): Mesenchymal neoplasia and congenital pulmonary cysts. Pediatr Radiol 9: 179–182.

Willius FA (1937): Cardiac hypertrophy and failure secondary to diffuse, bilateral congenital cystic disease of the lungs. Proc Staff Meet Mayo Clin 12:572–575.

Wilson SK, Moore GW, Hutchins GM (1978): Congenital cystic adenomatoid malformation of the lung associated with abdominal musculature deficiency (prune belly). Pediatrics 62:421–423.

Womack NA, Graham EA (1941): Epithelial metaplasia in congenital cystic disease of the lung. Its possible relation to carcinoma of the bronchus. Am J Pathol 7:645.

Zangwill BC, Stocker JT (1993): Congenital cystic adenomatoid malformation within an extralobar pulmonary sequestration. Pediatr Pathol 13:309–315.